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The Potential Role of Sleep in Promoting a Healthy Body Composition: Underlying Mechanisms Determining Muscle, Fat, and Bone Mass and Their Association with Sleep

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Keywords

Body composition · Sleep architecture · Slow wave sleep · Tissue metabolism · Growth hormone

Abstract

Sleep plays an essential role in human life. While sleep is a state elicited by the brain, its vital role reaches beyond maintaining brain health. Unhealthy sleeping habits have been associated with increased risk for inflammation, obesity, or diabetes. Evidence is emerging that sleep guides processes playing an important role in promoting the regulation of endocrine function involved in tissue regeneration and tissue remodelling. Thereby, sleep presumably is a critical factor contributing to the balance of core body tissues: bone, fat, and muscle mass. Given the increasing prevalence of various chronic diseases and comorbidities due to unhealthy lifestyle choices, sleep could be a key target to promote a healthy body composition up until old age. Here, we review the potential role of sleep and its underlying brain oscillations in body core tissues turnover. Specifically, we discuss potential underlying mechanisms linking sleep to body

composition, both during rest and under challenging conditions. Among other described pathways, we highlight the possible role of the growth hormone that was found to be involved in the homeostasis of all core body tissues and has been strongly linked to brain activity dominating deep sleep, the so-called slow waves. Finally, we formulate important questions to be addressed in future research on the effect of sleep on body composition and specifically emphasize the importance of intervention studies to move from correlative to causal evidence.

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Introduction

Spending around one-third of a lifetime sleeping, it is undeniable that sleep is essential to human life. While research revealing structural characteristics of sleep as for instance the distribution of sleep stages or underlying brain oscillations has been progressing with high speed, the functions of sleep remain poorly understood. Several studies have identified a potential role of sleep for brain

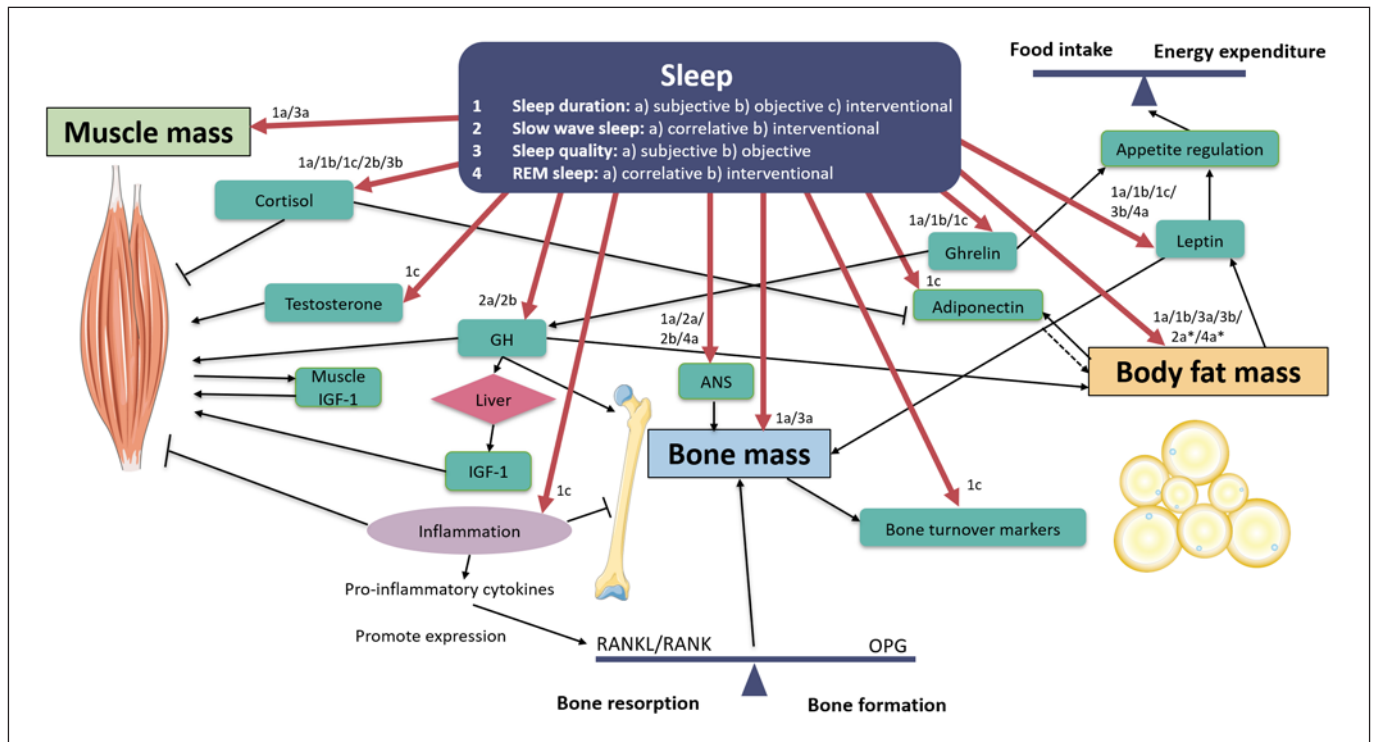


Fig. 1. Summary of potential pathways involved in the regulating body composition parameters and their relation to different sleep variables. Despite the directionality of the arrows, the direction of the relationship is not in all cases conclusively clarified. The numbers represent the sleep characteristic: 1 = sleep duration, 2 = slow wave sleep, 3 = sleep quality, and 4 = REM sleep. The letters a, b, and c indicate whether sleep was reported subjectively or objectively or whether the association was shown in an experimental study design (e.g., sleep intervention). Latter may already point to a causal relationship. Multiple numbers indicate a certain pathway or a molecule to be related to >1 sleep variable. Muscle mass (left),

bone mass (middle), and body fat mass (right) are all regulated by various mechanisms (black arrows pointing to the respective mass). *An association on body fat mass was not shown directly, but on body mass index instead. REM, rapid eye movement; GH, growth hormone; IGF-1, insulin growth factor 1; ANS, autonomic nervous system; RANK, receptor activator of NF- κ B; RANKL, receptor activator of NF- κ B ligand; OPG, osteoprotegerin. Used creative commons: adipocytes: by Database Center for Life Science (DBCLS) – License: CC BY; bone: by Servier Medical Art – License: CC BY; muscle: by Servier Medical Art – License: CC BY.

health, such as cleaning away toxic by-products [1, 2], synaptic plasticity [3–6], and memory consolidation [1, 7–13]. In addition, an increasing number of studies point towards the fact that the restorative functions of sleep are not restricted to the brain only, but are also important for peripheral body functions, such as immune [14], cardiovascular [15], and metabolic functions [16]. By this time, it is generally accepted that sleep is an integral factor for people’s health. Yet the underlying mechanisms and the specific involvement of sleep in peripheral body processes are still not fully understood.

The proportion of fat-free mass and fat mass in the body, often referred to as “body composition,” is a key aspect determining overall health [17–19]. Evidently, nutrition and physical activity are essential factors determining body composition and have been studied thoroughly for

the last decades. Sleep, on the contrary, has gained much less attention as a central regulator of body composition, despite its pivotal role in regulating mass turnover [20–22]. Therefore, this review aims to summarize current evidence on how sleep affects processes that build and remodel body composition under physiological conditions and upon system challenges, for example, through exercise or injury. Identifying and understanding the involvement of specific aspects of sleep in processes that determine body composition is key to identifying targets for prevention or treatment of pathological states of body composition. The present work starts by summarizing components of body composition and an introduction to sleep and sleep architecture. Thereafter, we will review existing literature on the association between sleep and aspects of body composition (muscle mass, fat, and bone

density) with a focus on a physiological mass turnover as well as on studies investigating the role of sleep in the respective processes, which are summarized in Figure 1. Considering situations of intended change in body composition, a short paragraph will be devoted to the importance of sleep related to exercise, weight loss, and fracture healing. Finally, current limitations and items for a research agenda will be discussed. Taken together, this work aims to identify potential pathways that are regulated through sleep quality and quantity and may play a central role for body composition. However, the mechanisms discussed in this review are likely not complete and we assume that some pathways and processes linking sleep and body composition are not even known yet.

Body Composition

Body Composition and Health

Body composition has repeatedly been shown to be central to health and disease, although its importance often only becomes apparent in pathological states. Body fat, for example, is a complex tissue with critical metabolic and endocrine functions by for instance releasing hormones regulating energy expenditure [23]. However, when present in excessive amount as in obesity, its effect on health is no longer beneficial. In fact, cardiovascular diseases [24], hepatic steatosis [24], insulin resistance [24], neurological disorders [25], and cancer [24] can all occur comorbid to obesity and drastically reduce life expectancy. Furthermore, low muscle mass, resulting from an imbalance between muscle protein synthesis and muscle protein breakdown, results in muscle atrophy [26], which at a later stage can result in detrimental outcomes such as disability, decreased quality of life, and increased mortality [27, 28]. Finally, decreased bone mass known as osteopenia can further progress to osteoporosis, a state of low bone mineral density, and an increased rate of bone resorption [19, 29]. Osteoporosis is an important risk factor for bone fractures and increased risk of falling [30, 31]. Obesity, muscle atrophy, and osteoporosis are all representing unique unhealthy changes in body composition parameters and put an immense burden on the health of individuals as well as on health care costs [32]. Therefore, finding a means to keep body composition in a healthy range or to improve pathological alterations of body composition is of great interest. Besides the well-known importance of healthy nutrition and physical activity for body composition [33, 34], sleep with its restorative functions is likely to be critically involved.

Body Composition Assessment Methods

To diagnose healthy and pathological states of body composition, dual energy X-ray absorptiometry (DXA) is currently the reference standard, providing precise assessments of core body tissues [35]. Less expensive but also less accurate alternatives to DXA are bioelectrical impedance analysis (BIA), waist circumference, waist-to-hip ratio, or the body mass index (BMI), which are commonly used assess body composition parameters [36]. Although BMI is the most widely used measure in population studies, it has clearly some limitations. BMI does, for example, not consider where the fat is located, which in some situation is the key factor influencing disease risk. For instance, as the visceral adipose tissue is known to be more closely associated with cardiovascular risk than the subcutaneous adipose tissue, assessing that waist circumference or waist-to-hip ratio could be beneficial over BMI. However, as on population level the BMI is a valid construct correlating well with measures of body composition and comorbidities from obesity, BMI is still the most widely used obesity measurement in the general population [37, 38].

Sleep

Sleep Regulation

Sleep regulation is governed by 2 interacting processes, the circadian and the homeostatic processes, a bimodal regulation that is commonly explained by the “2 process model” [39, 40]. The homeostatic process, called process S, refers to the continuous build-up of sleep pressure during wake time. For this pressure to subside, sleep is required no matter at what time of the day/night. On the other hand, process C, a process controlled by the circadian pacemaker, is independent of sleep and rises and falls periodically. The circadian pacemaker orchestrates many of the body’s internal biological processes, including core body temperature, feeding patterns, and hormone production in a highly rhythmic pattern [41]. Although processes S and C are known to act mostly independently of each other, they both influence sleep and sleep patterns in a highly complex and additive manner [42]. While both sleep and the circadian rhythm are involved in metabolic functions, here we solely focus on effects caused by sleep itself. Controlled approaches aiming to identify the contributions of sleep are sleep restriction or sleep modulation studies (e.g., modulation of specific aspects of sleep architecture) [43–45]. These studies compare a molecule or a hormone of interest in a sleep-de-

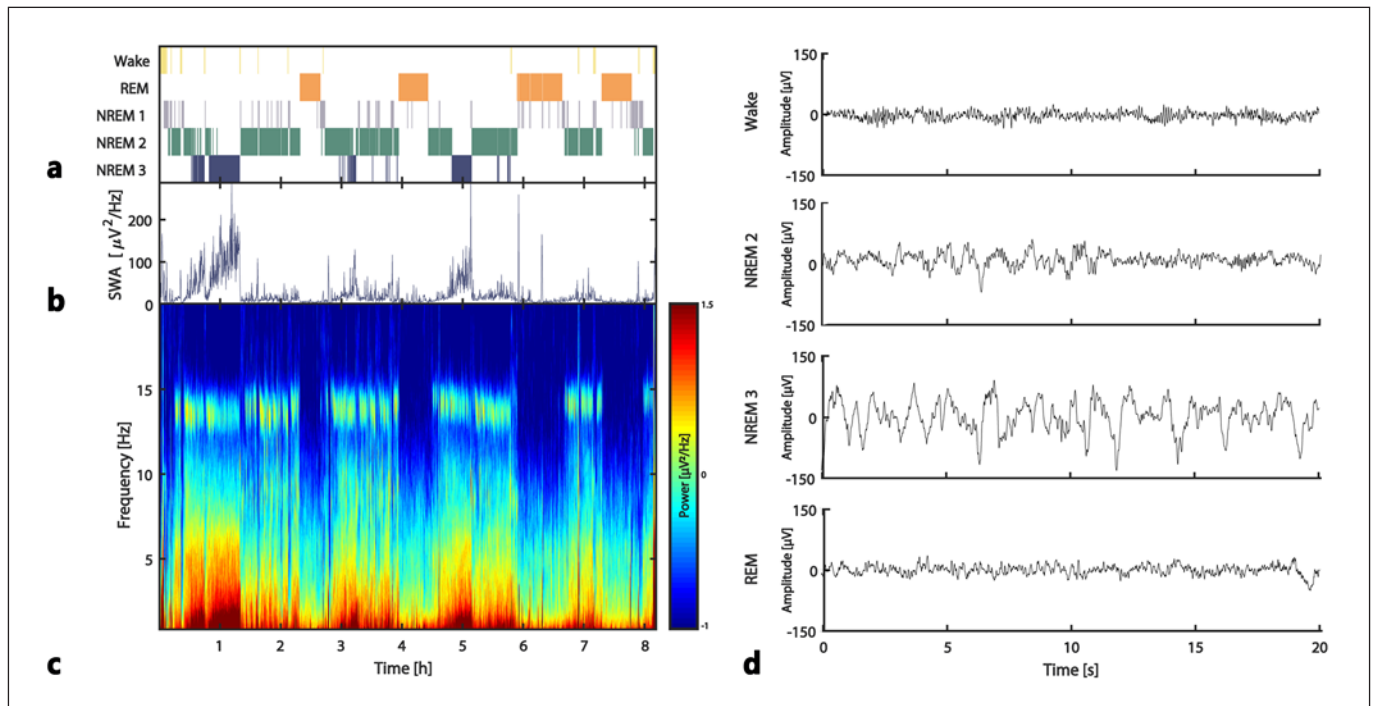


Fig. 2. **a** Hypnogram showing distribution of sleep stages (wake, REM, and NREM sleep stages 1, 2, and 3) across an exemplary subject. **b** SWA (0.5–4.5 Hz) of electrode Pz of full night sleep. **c** Spectrogram of electrode Pz across full night. **d** Schematic illustration of the EEG activity of a frontal electrode to mastoid abbreviation (F3A2) for wake, NREM2, NREM 3 (SWS), and REM sleep. High-amplitude slow waves dominate during NREM 3. SWA, slow wave activity; REM, rapid eye movement; NREM, non-rapid eye movement.

prived/modulated condition to a sleep-sufficient/unmodulated condition [16, 46, 47]. However, in some cases, a clear distinction between sleep and circadian contributions is not possible and those cases will be addressed in the respective References of the review.

Sleep Architecture

A major breakthrough in the field of sleep science was the development of the electroencephalogram (EEG), which enabled researchers to reliably measure activity in the brain mediated by changes in the electrical activity of large populations of neurons [48]. The EEG allows to detect changes in brain activity between wake and sleep, and also between sleep stages [49], as illustrated in Figure 2d. Those synchronized brain activity patterns at specific frequencies (seen as EEG rhythms) can be categorized into oscillation bands. Human nocturnal sleep periods are hallmarked by a cycling pattern between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, with an approximate duration of 90–120 min per sleep cycle [49, 50]. NREM sleep is characterized by sleep spindles (transient thalamocortical oscillations between

11 and 16 Hz) and slow waves [51]. These slow waves are high amplitude, low-frequency waves (e.g., <4 Hz), and an increase in number and size as sleep deepens. The transition from NREM stage 2 (N2) into NREM stage 3 (N3), the deepest stage of sleep, is characterized by the presence of slow waves during >20% of the time [49]. This stage is therefore also termed slow wave sleep (SWS). The distinction between REM sleep and wake brain activity is difficult because of the absence of dominant oscillations. However, REM sleep is characterized by decreased muscle tone, reflecting muscle atonia, and REMs, that can both be identified using electromyogram and electrooculogram, respectively, in addition to the EEG [49, 52]. As the night advances and the morning approaches, the length of REM sleep increases, while the NREM stages become shorter, representing a significant change of the proportion of REM/NREM sleep within a sleep cycle across the night [53]. An exemplary sleep architecture of a night is illustrated in Figure 2a. Besides some natural changes in sleep architecture across consecutive nights, particularly healthy ageing is associated to affect the duration and proportion of sleep stages. Older age is associ-

ated with a markedly reduction of amount and extent of SWS [54, 55]. Thus, the physiological decline in total sleep duration with increasing age makes sleep in the elderly a suitable model to study the relationship between SWS and body composition. In addition to quantitative changes in SWS, sleep gets more fragmented and shorter with increasing age [56], whereas the percentage of REM sleep remains fairly stable [57].

Sleep Assessment Methods

The gold standard for the reliable estimation for sleep and wake times, but also the assessment of sleep architecture and the detection of sleep oscillations is polysomnography (PSG) [58]. This method involves several measures of sleep, including brain activity measured by EEG, muscle activity (electromyogram), and eye movements (electrooculogram). These recordings can be accompanied by heart activity and respiratory function, for example, for sleep disorder screening such as sleep apnoea [58]. Since PSG assessments are costly, complex, and require expensive equipment, studies often approximate sleep and wake duration as well as sleep quality (e.g., sleep continuity) with actigraphy [59]. This method involves a wearable device usually worn on the wrist or ankle that records body acceleration. Therefrom, together with mathematical algorithms, wake times, sleep times, and rough approximations of sleep stage parameters can be calculated [60]. Besides objective sleep assessments, perceived sleep quality and quantity can be assessed by questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), which includes different items and finally provides a global score with higher values indicating worse sleep [61]. Collectively, questionnaires and actigraphy are often assessed in home settings, whereas PSG is usually carried out in a sleep laboratory [59].

Sleep and Muscle Mass

Skeletal muscle mass is, apart from its key role in locomotion, also a metabolic organ that is essentially involved in whole-body homeostasis [62–64]. Skeletal muscles in a healthy adult comprise about 38% of total body mass in men and approximately 30% in women [65]. A significant loss in muscle mass and strength with increasing age is defined as sarcopenia, entailing a loss of functionality, which may result in disability and an increased risk for chronic diseases including insulin resistance, fatigue, and mortality [66–69]. Therefore, finding means to preserve muscle mass with old age may improve musculoskeletal and overall health. Besides optimized nutritional and

physical activity regimen, prioritizing healthy sleep could aid in preserving muscle mass.

The influence of sleep on muscle mass has been the focus of several studies reporting an increased prevalence for lower muscle mass and sarcopenia in short sleepers as well as those who reported habitual poor sleep quality [70–77]. Besides muscle mass, poor subjective sleep quality and sleep efficiency were also associated with decreased grip strength, underlining the relevance of sleep for functional aspects of muscle mass [72]. Sleep deprivation is proposed to influence the balance between synthesis and breakdown of muscle proteins by increased proteolysis [78], which ultimately leads to a loss of muscle mass. This view is supported by the observation of higher urinary protein secretion after 72 h of sleep deprivation, which is characteristic for enhanced proteolytic processing [79]. A study directly highlighting the negative effects of short sleep on body composition showed that while on a 14-day calorie-restricted diet, the change of fat and muscle mass significantly varied with the allowed sleep time, that is, 8.5 h or 5.5 h (sleep restriction). More specifically, weight loss was comparable in both groups (~3 kg). However, participants in the short sleep condition showed a 55% lower decrease in fat mass and a 60% higher decrease in muscle mass than the volunteers that had the 8.5 h sleep opportunity per night. The longitudinal experimental design implies that during sleep, key processes involved in muscle metabolism occur, which are required to preserve muscle mass during a calorie-restricted diet [80]. Short sleep may therefore undermine the efficacy of the diet-induced loss of body fat.

Apart from experimental studies investigating the effect of partial or total sleep restriction on muscle mass, observational studies of sarcopenic patients provide useful information on the link between muscle mass metabolisms and sleep. As proposed by Piovezan et al. [81], the underlying mechanisms for age-related sarcopenia may be associated with changes in sleep patterns. Their hypothesis builds on the evidence that older adults show decreased sleep time and efficiency along with a significant decrease in the amount and intensity of SWS. This decrease is paralleled by a dysregulation of the somatotropic, gonadal, and corticotropic activity as well as glucose metabolism, all of which are critically involved in muscle metabolism [81, 82].

Underlying Mechanisms

To maintain a constant mass of muscle tissue, a balance between muscle anabolism mediated by protein synthesis and muscle catabolism is required. Any imbalance,

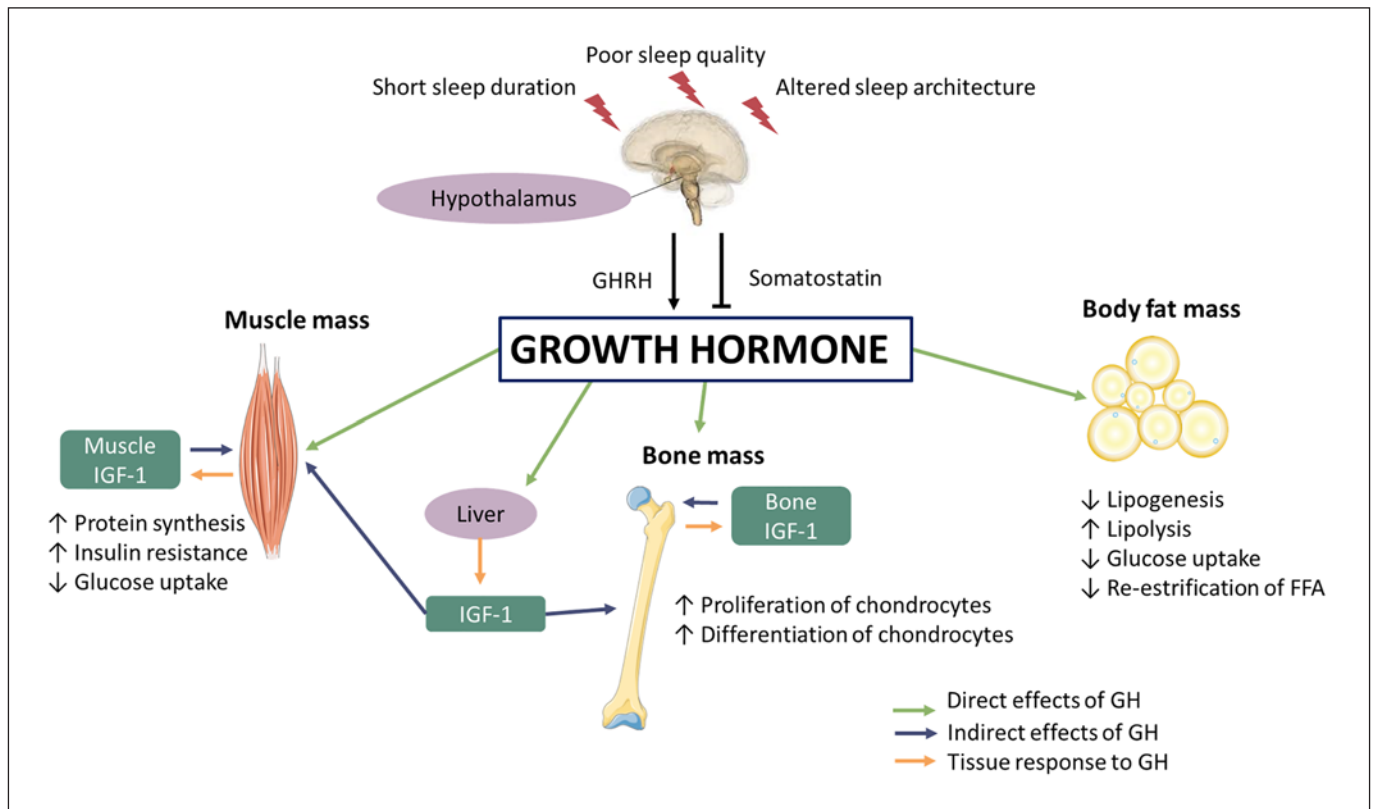


Fig. 3. GH is critically involved in the regulation of muscle-, bone, and body fat mass and is affected by different types of sleep disturbances. GH is known to act by 2 different mechanisms, directly by binding to its receptor on target tissues and ultimately leading to the induction of signalling cascades or via its indirect mode of action via IGF-1. IGF-1 is secreted mainly by liver but also by other tissues including bone and muscle in response to GH. While in bone and muscle tissue both modes of actions are important, the

action of GH on body fat is suggested to be mediated by its direct effect only. Used creative commons: brain: by Nickbyrd – License: CC BY-SA; adipocytes: by Database Center for Life Science (DBCLS) – License: CC BY; bone: by Servier Medical Art – License: CC BY; muscle: by Servier Medical Art – License: CC BY. GH, growth hormone; IGF-1, insulin-like growth factor 1; GHRH, growth hormone-releasing hormone.

especially over longer time periods, leads to muscle hypertrophy when protein synthesis dominates, or muscle atrophy when protein degradation is prevalent [83]. In the following paragraphs, we first identify pathways involved in the synthesis and breakdown of muscle proteins and second highlight whether and how these are modulated by sleep. A summarizing graphical overview of potential underlying mechanisms discussed below is presented in Figure 1.

Insulin-Like Growth Factor 1/Growth Hormone

Growth hormone (GH) is a central player in the promotion of somatic growth and has a pivotal role in metabolism including the regulation of glucose, lipolysis, and protein synthesis [84]. GH can either act directly or indirectly via the GH-induced insulin-like growth factor

1 (IGF-1) secretion, both mechanisms being shown to stimulate muscle protein synthesis [84]. Primary evidence for the muscle mass stimulating effect of GH comes from the observation that the treatment of GH-deficient subjects with GH could significantly increase skeletal muscle mass [84]. Similarly, the administration of supra-physiological levels of GH with and without additional exercising in healthy adults has also repeatedly been shown to increase lean body mass [85–87]. However, variations in physiological levels of GH do not modulate muscle growth in adults [88], whereas cumulative deficits over longer time periods, as observable in older adults [89], could negatively affect muscle metabolism. Thus, age-related changes in body composition are hypothesized to be related to or caused by decreased levels of GH, a concept known as “somatopause” [90] (see Fig. 3).

When investigating the effect of sleep on the GH/IGF-1 axis, GH rather than IGF-1 secretion is of central importance. The secretion pattern of GH has been shown to follow a 24-h pattern, with sleep being an important window of most pronounced GH release [84]. A high GH release can specifically be observed soon after sleep onset temporally associated with the first episode of SWS [91, 92]. SWS as well as GH levels show a significant gradual decline with increasing age [93]. Moreover, GH secretion was shown to be highly associated with the percentage of SWS even after controlling for age [93]. Therefore, SWS seems to play a key role in the regulation of GH secretion. These observations are in line with previous findings from a study in which van Cauter et al. [94] showed that stimulation of SWS by gamma-hydroxybutyrate (GHB) doubled the secretion of GH in the first 2 h after sleep onset. In contrast, Besedovsky et al. [95] reported no significant difference of GH secretion when they acoustically enhanced slow waves and speculated that the increase in slow wave activity (SWA) may have been not strong enough to affect GH secretion in a young population. Furthermore, the lack of an effect on GH secretion might be due to its secretion being controlled by other aspects of sleep [95]. More specifically, while sleep seems to be the primary regulator of GH release, a circadian contribution could likewise be at play [96]. For instance, observations from a study investigating GH concentration in permanent night- and daytime workers support the presence of a relevant circadian regulation. Even though both groups showed similar amounts of SWS, night-time workers had a lower GH secretion during their daytime sleep than daytime workers during their nightly rest. The total amount of GH secreted over 24 h, however, did not differ between the groups, suggesting a potential compensatory mechanism [96]. So far, we have only focused on possible mechanisms on how sleep affects GH. However, there is evidence for a reciprocal relationship. From animal [97] and human studies [98, 99], it is known that the growth hormone-releasing hormone (GHRH), released by the hypothalamus, stimulates NREM sleep intensity and/or duration and SWS in particular [98, 100, 101]. In contrast, preliminary findings on the effect of GH on sleep indicate that GH itself mainly promotes REM sleep [102, 103]. This implies that patients with GH deficiency (GHD) (e.g., Sheehan syndrome, GHD of pituitary origin), where low levels of GH lead to an impaired negative feedback mechanism on GHRH and subsequently to excessive GHRH [104], would have longer SWS and less REM sleep than healthy controls. In situations where the GHD originates in the hypothala-

mus (e.g., Prader-Willi syndrome), a different phenotype is expected: due to a disrupted hypothalamic function, GHRH levels are low together with GH levels. Consequently, decreased SWS and REM sleep compared to age- and sex-matched controls are expected. However, while the expected alterations in sleep were repeatedly observed [98, 99, 105, 106], only few studies have been able to show a reversibility of the altered sleep characteristics through GH administration yet [102, 107, 108].

In conclusion, apart from the role of sleep in regulation of GH levels, the effect of GH/GHRH on sleep characteristics also warrants attention because clinical and experimental data support the presence of a reciprocal interaction between GH and sleep physiology. Given the inconclusive results, experimental studies investigating the bidirectional relationships and underlying mechanisms are needed. Due to the fact that patients with GHD often have increased fat mass and reduced lean mass [109–111], they might represent an interesting model to additionally study how the altered hormone status influences body composition.

Testosterone

Testosterone is not only influencing male secondary sex characteristics but also has anabolic muscle effects [112]. Various mechanisms how testosterone may induce muscle hypertrophy have been suggested, including the commitment of pluripotent stem cells to differentiate into cells of the myogenic type [112]. Studies investigating how testosterone secretion patterns are affected by sleep have mostly been conducted in men only [113]. Nonetheless, testosterone was shown to play a central role in female muscle and bone anabolism too [113]. In elderly women, higher levels of circulating testosterone have directly been associated with increased lean body mass [114], thereby supporting evidence that the effect of testosterone is not restricted to men only. Because women can also increase muscle mass despite having extremely low concentrations of testosterone, this implies that supraphysiological rather than physiological doses of testosterone are responsible for the shift towards muscle anabolism [115, 116]. The circadian component in the secretion of testosterone is responsible for to levels peaking in the early morning and its decrease during the day [117–119], while an ultradian rhythm leads to the burst-like secretion pattern of testosterone in 90-min intervals [120]. Starting after sleep onset, testosterone levels gradually rise until they reach a plateau coinciding with REM sleep onset [121]. Although the rhythm of nocturnal testosterone secretion seems to be related to the cycling be-

tween REM and NREM phases [122], Evans et al. [123] observed that REM sleep does not directly lead to a production of testosterone. Axelsson et al. [124] observed a rise in testosterone during daytime sleep, with decreasing levels upon awakening, implying that testosterone levels in healthy young men are mainly regulated by sleep and weakly by circadian influences. In addition, a 1-week sleep restriction in healthy men (<6 h sleep/night) led to significantly lower testosterone levels than a rested condition (>8 h sleep) [125]. As ageing is associated with decreased testosterone levels in men and women, testosterone administration to re-establish physiological levels can be considered to prevent the age-related loss in muscle mass [116, 126–133]. The significant decrease of sleep duration as well as sleep efficiency and especially percentage of SWS with age may at least partially explain the reduced testosterone secretion in elderly.

Cortisol

Contrary to the anabolic hormone testosterone, cortisol shows catabolic effects for muscle hypertrophy [134]. Cortisol, commonly called “stress hormone,” is secreted in response to many types of physiological and psychological stress [135], while to some extent required, supra-physiological levels of cortisol have been suggested to modulate muscle protein metabolism through increased catabolism [136] and decreased synthesis of muscle proteins [137]. Pathological hypercortisolism as observed in Cushing’s syndrome [138] shows characteristic proximal muscle weakness among other symptoms associated with an unfavourable effect on body composition such as abdominal fatty tissue deposits or bone loss [138]. Biopsy investigations of muscular tissue from patients with Cushing’s disease also revealed morphological changes in muscles, seen as damaged mitochondria in muscular tissue, malformations of muscle fibres, and wide interfibrillar spaces [139].

Since cortisol secretion is enhanced under stress [135], one might expect that NREM sleep, as a relaxing state of human body and brain, is associated with decreased cortisol levels. However, varying cortisol levels between sleep and wake [140] can be a result of either the circadian control of hormone release, the influence of sleep itself, or even a combination of both. Therefore, controlled experiments to elucidate the respective influence of these 2 processes are needed. Evidence for the regulation by a circadian mechanism suggests that the release of cortisol is under the control of the central and peripheral circadian clocks. In turn, this leads to a peak of cortisol levels at the start of the activity phase, which, for diurnal organisms

such as humans, is in the mornings [141]. However, sleep itself also contributes to cortisol secretion and the regulation of plasma cortisol concentrations [142]. An inhibitory effect of sleep leading to a decreased secretion of cortisol was found independent of sleep timing within the circadian rhythm in a 4-day sleep restriction protocol including sleep phase shifts and total sleep deprivation [143]. Further evidence showed that cortisol levels were significantly higher after 36 h of sleep deprivation than control and recovery nights [144]. Taken together, short sleep and total sleep deprivation are associated with increased cortisol levels independent of the circadian phase [143–145]. Apart from sleep duration, several studies investigated whether an association between sleep quality and cortisol levels exists. Poorer sleep quality, subjectively assessed by PSQI and objectively by actigraphy, was associated with a smaller early-morning cortisol decline and a slower rate of cortisol decline later in the day [146]. Specifically, SWS was shown to suppress the release of cortisol [14], with a variation in the secretion pattern that is temporally associated with the power spectral density in the slow wave EEG band (SWA) [147]. SWA across an exemplary night is illustrated in Figure 2b. Furthermore, selective enhancement of slow waves through acoustic stimulation led to a significantly reduced cortisol concentration during the first hour of stimulation, with a significant reduction already after 5 min of stimulation [95]. These observations are comparable to previous results from studies in which SWA was enhanced by pharmacological agents [106, 148]. Grimaldi et al. [149] reported significantly reduced evening-to-morning increases in cortisol when SWA was increased using acoustic stimulation compared to sham stimulation. However, they did not find a change in total cortisol levels after sleep following acoustically enhanced SWA. It should be noted though that, contrary to other studies, blood samples for cortisol testing were only drawn in the evening prior to sleep and in the morning [149]. Thus, cortisol levels may already have had risen when the blood sample was drawn in the morning and thereby the lowest concentrations may have been missed.

Inflammation

While so far focusing on hormones and peptides, the presence of a chronic low-grade inflammatory environment is likely to be another mechanism, which relates muscle mass metabolism to sleep [150]. As reviewed by Beyer et al. [150], there is a consistent association of age-related sarcopenia and chronic low-grade inflammation [150]. Both systemic [151, 152] and tissue-specific [153–

156] inflammatory markers were negatively associated with muscle mass and inflammation-related pathways. Moreover, numerous total and partial sleep restriction studies exist, showing an increment in markers for acute inflammation such as interleukin-1 (IL-1), tumour necrosis factor alpha (TNF- α), IL-6, and C-reactive protein (CRP) in response to sleep manipulation in humans [157]. Negative effects of inflammatory environments have mostly been examined in relation to cardiovascular disease. However, enhanced expression of these cytokines is also known to interfere with other physiological pathways such as impaired muscle anabolism or increased muscle protein breakdown [158]. TNF- α as one example of a pro-inflammatory cytokine that is sensitive to sleep restriction is known to play a critical role in cachexia, a pathological condition causing ongoing muscle loss [159]. The underlying mechanism involves NF- κ B transcription factors, which are expressed in skeletal muscle, where they act as effect mediators of pro-inflammatory cytokines. In several sleep restriction studies as for instance by Irwin et al. [160], peripheral NF- κ B levels were compared between baseline sleep, partial sleep deprivation, and recovery sleep. Results revealed a significantly increased NF- κ B concentration in the morning after partial sleep deprivation compared to the other conditions [160]. Similarly, TNF- α receptor 1 and IL-6 were elevated following experimentally induced total sleep restriction [161]. Moreover, elevated CRP levels, a strong predictor for cardiovascular morbidity, were observed following partial and total sleep restriction compared to a sufficient sleep condition [162]. Taken together, several studies found an increment of pro-inflammatory cytokines during nights of short sleep. However, whether these changes in inflammatory levels due to impaired sleep translate into impaired muscle protein synthesis, both in the short and long-term, remains to be investigated.

Limitations and Implications

Concentrations and secretion patterns of various key players in muscle metabolism have been shown to be related to or affected by sleep. In addition, impaired sleep has been linked to reduced muscle mass and function [72, 163, 164], implying that sleep potentially affects muscle homeostasis. Yet, studies that directly link sleep and muscle mass as well as additionally provide a causal link of any of these pathways are still lacking. A positive influence of sleep on muscle anabolism is supported by studies that followed a sleep restriction protocol [80, 165]. However, they solely assessed the adverse effect of an insufficient amount of sleep and never examined whether specific

sleep cycles, sleep-specific oscillations, or certain sleep stages such as REM or NREM contribute to the observed effects. While research on the mechanism how GH and cortisol secretion are related to slow waves has been conducted, further research is needed inspecting the relevance of sleep macro- and microstructure on proposed mechanisms that lead to impaired muscle metabolism. Moreover, the correlation between a significant decline in SWS and the development of sarcopenia observable in elderly requires further investigation. In addition, sleep may become even more important for the metabolic processes during situations challenging muscle homeostasis (e.g., exercise) than baseline physiological conditions [163, 164].

Sleep and Body Fat Mass

Excessive fatness, as observable in obesity, has become a major health problem across the world [166]. An excessive accumulation of body fat mass is often thought to be a consequence of an unhealthy diet and low levels of physical activity, whereas poor and short sleep are rarely considered as risk factors.

Several studies reported correlations between indices of fat mass and insufficient sleep [167–172] consistently across all age groups [173–179]. Interestingly, a trend towards higher BMI with less hours of sleep has been observed in men, whereas the relationship in women has been found to be U-shaped [180], suggesting that the dose-response relationship is influenced by gender. In a large-scale study including 1,024 volunteers, a minimal BMI was found for a nightly sleep duration of 7.7 h [176], which is in line with the recommended 7 h–9 h sleep/night for adults [181]. The identification of underlying mechanisms linking sleep to BMI is of current interest and not yet completely resolved. However, endogenous mechanisms such as appetite regulation by hormones and the endocrine control of energy expenditure are likely to be involved [182]. Another potential mechanism how short sleep may lead to weight gain involves the change in food choices or the increased wake time in an obesogenic environment [183], leading to increased energy intake [182]. Most likely, no single pathway fully explains the association between short sleep and high BMI, but rather various mechanisms are simultaneously at play. Jurado-Fasoli et al. [184] observed an association between body fat mass percentage, assessed by DXA, and poor subjective sleep quality in sedentary middle-aged adults, which did not remain significant after including

sex or sex and age in the model. Neither subjective sleep efficiency nor accelerometer-assessed wake after sleep onset correlated with body fat mass percentage [184]. In contrast, lower sleep efficiency measured by actimetry was found to be associated with higher fat mass assessed by BIA in students [185]. Interestingly, this association differed between men and women. The observation only held true for sleep on workdays in women, and for sleep on weekend days in men. This unexpected difference led to the hypothesis that poor sleep on workdays in women was tightly related to low levels of physical activity on these days. However, poor sleep efficiency in men on free days was observed to occur simultaneously with a higher dietary fat intake [185]. Other studies assessing body composition by BIA found single components of PSQI-assessed subjective sleep including sleep latency, sleep disturbances, and daytime dysfunctions to be associated with body fat mass [186]. Similarly, total sleep duration reported on a questionnaire correlated with fat mass assessed by BIA in young athletes [187]. Although the authors do not discuss potentially underlying mechanisms in detail, poor sleep patterns are hypothesized to alter endocrine function [186] towards a pro-fat-deposition hormonal pattern such as increased morning cortisol, which in turn increases the amount of body fat [185, 187].

Rao et al. [188] further linked fat mass to aspects of sleep architecture. BMI, but not the percentage of total body fat mass measured by DXA, was shown to be significantly associated with SWS percentage. As a possible limitation and reason for the lack of a relationship, the authors suggest that abdominal rather than total body fat might be associated with SWS, with only latter examined in this study [188]. Another study aimed to determine gender differences in the context of body composition and sleep patterns [189]. Detailed analyses of sleep architecture revealed a significant negative correlation between SWS percentage and percentage of body fat mass in women but not in men [189]. Apart from SWS, a population-based study found a reduction in REM sleep to be associated with obesity in women [190]. Similar results were obtained in children and teens, showing time spent in REM state to negatively correlate with overweight [191]. Chronic insomnia, which is considered the most prevalent sleep disorder [192] and that is characterized by a lack of sleep or inability to sleep [193], has also been associated with future weight gain [175, 194] and obesity [176, 195]. Moreover, a meta-analysis found that patients with insomnia had a higher risk of suffering from hypertension, hyperglycaemia, and obesity, which are the lead-

ing symptoms of the metabolic syndrome [196]. The causes of insomnia as well as its association with an altered body composition are complicated and diverse. Altered secretion profiles of pro-inflammatory cytokines [197], ageing [198], menopause, stressful events, and depression are all contributing factors to the hyperarousal and finally to insomnia [199]. Although the association with obesity is still unclear, it has previously been hypothesized that a hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis and a dysregulation of hormones that regulate energy homeostasis might be involved [200, 201].

Taken together, poor subjective sleep quality was repeatedly shown to be associated with unfavourable changes in body fat mass. Yet, the underlying mechanisms are insufficiently explored, but appetite regulation, energy expenditure, and secretion of hormones are likely to be contributing aspects. Little is currently known about whether specific sleep stages may have an impact on body fat mass accumulation and further investigations of extended duration are needed, also considering gender as a relevant factor.

Underlying Mechanisms

In the following paragraphs, we will discuss potential underlying mechanisms linking sleep to excessive fat tissue. An overview of those mechanisms is presented in Figure 1.

Appetite Regulation

One mechanism relating sleep to excessive accumulation of body fat mass might be the pattern of food intake, which is driven by appetite, regulated by 2 opposing hormones leptin and ghrelin [202].

Leptin

Leptin is a hormone that is produced by adipocytes and informs the body about its energy status. It has gained special interest in the context of sleep because its secretion follows a circadian rhythm that is further influenced by sleep and fasting [179, 203]. Under normal conditions, leptin levels increase during sleep until the peak is reached at around the midpoint of sleep followed by a gradual decrease until mid-afternoon [177]. Reduced leptin levels resulting from chronic starvation enhance the drive to eat [204].

Several cross-sectional studies investigating whether there is a correlation between sleep duration and leptin levels revealed inconclusive results. While Knutson et al. [205] did not find a correlation between habitual sleep

duration assessed by actigraphy, a large population-based study by Taheri et al. [176] revealed that short habitual sleep duration was associated with decreased leptin levels. Along these lines, several studies investigated whether sleep restriction or sleep deprivation affects leptin levels, again revealing conflicting results. Several studies using total sleep deprivation showed a decreased amplitude of the variation of leptin levels over 24 h [178, 206, 207]. For example, one study found that sleep restriction to 4 h compared to 12 h led to a 19% decrease in the nocturnal amplitude of leptin levels [207]. In contrast, more recent findings observed leptin concentration to either increase in response to experimental sleep restriction [208] or remain unchanged [209]. Constant measurement of leptin levels during 38 h of wakefulness in a constant routine protocol aimed to disentangle the specific contributions of the endogenous circadian rhythm and behavioural factors such as sleep on leptin levels. Leptin concentrations increased linearly during the period of wakefulness without a modulation by circadian phase, whereas a significant decrease in leptin during recovery sleep has been observed [179].

The contradictory findings about the association of sleep duration and leptin levels may be explained by the fact that leptin is rather a long-term signal [210]; thus, a single night of short sleep does not lead to an immediate decrease in leptin levels. In line with this notion, chronic short sleep, however, is associated with significantly decreased leptin levels. Moreover, sleep loss affects mean leptin levels over 24 h as well as the amplitude of the leptin secretion profile [178, 206, 207] rather than morning serum leptin.

Only little research has been conducted on how sleep architecture is associated with the secretion of leptin. Olson et al. [211] focused on the percentage of REM sleep assessed by PSG and its association with leptin levels that were assessed before and after sleep, respectively. They found a higher percentage of REM sleep to be associated with a more pronounced overnight change in leptin, which is likely to contribute to an increased amplitude of 24 h leptin levels [211]. Based on findings from previous research, the amplitude of leptin concentration better predicts food intake than morning leptin concentration [212, 213]. Thereby, changes in circulating leptin may represent the link between the previously discussed association of REM sleep percentage with prevalence of overweight reported by Liu et al. [191] and Theorell-Haglöw et al. [190]. In contrast to the percentage of REM sleep, no significant relationship between any NREM sleep stage and changes in leptin levels was observed [211].

Ghrelin

Another peptide involved in the regulation of appetite and food intake is ghrelin. Ghrelin is primarily secreted from the stomach and has been shown to increase appetite thereby leading to increased food intake in humans [214]. Under normal conditions, ghrelin secretion follows a circadian and ultradian pulsatile pattern, with the peak of ghrelin concentration occurring during the night [203]. However, this regulation only applies to lean and not obese subjects [203]. Observational studies investigating the association between sleep duration and ghrelin levels mostly showed ghrelin levels to be negatively correlated with sleep duration [176, 215, 216]. Experimental studies however show conflicting results as reviewed by St. Onge [217]. While some studies report an increase in ghrelin in the sleep deprived compared to the control group [218–220], others did not find any differences [221–223]. For instance, in a study where subjects were allowed to stay in bed for 4 h/night on 2 days followed by a bedtime of 10 h/night for another 2 days, researchers observed 28% higher ghrelin levels in the sleep-restricted condition than the 10 h bedtime condition [219]. Similarly, another study found increased ghrelin levels after one night of total sleep restriction compared to a sleep opportunity of 5 h using a crossover design. In-between ghrelin levels were observed in the third condition, in which volunteers had the opportunity to sleep for 7.5 h [218]. Thus, in contrast to leptin, ghrelin seems to be more sensitive to short-term sleep behaviour [176], which is in line with the fact that ghrelin is a rapidly acting hunger signal, whereas leptin is a long-term energy balance parameter [224]. The findings that sleep loss leads to alterations in endocrine levels which control food intake might be part of the link between short sleep and the risk of obesity. However, the conflicting results warrant large-scale controlled experiments. Different study regimes, sampling times, participant characteristics, and the complex interplay between hormones may contribute to varying results [182]. Furthermore, increased food intake following sleep curtailment has been consistently reported [182, 217]. Therefore, factors other than hormonal imbalance should be considered to explain the obesogenic effect resulting from short sleep [182].

Adiponectin

Adiponectin belongs to the group of adipokines and is specifically secreted by adipocytes, the cells of adipose tissue [225]. It is inversely correlated with the amount of adipose tissue and its concentration has been observed to decrease with the onset of obesity [226]. Recent evidence

from animal studies promises beneficial effects of adiponectin in terms of weight reduction and improvements in insulin sensitivity [227]. Therefore, the question is whether an intervention may lead to an increase of endogenous serum adiponectin and potentially promote a healthy weight management in humans. As one factor, sleep might modulate adiponectin levels through the HPA axis, which is sensitive to sleep. SWS might be of particular interest since an inhibitory effect of SWS on the HPA axis and subsequently on cortisol secretion has previously been reported [143]. In a study by Fallo et al. [228], administration of glucocorticoids such as hydrocortisone leads to an inhibition of adiponectin secretion in healthy males, supporting the fact that glucocorticoids affect adiponectin levels. Taken together, evidence suggests that experimentally induced enhancement of slow waves could lead to decreased glucocorticoid levels, which in turn results in higher adiponectin levels. However, there are numerous studies showing that glucocorticoid treatment led either to increased blood adiponectin concentrations [229–234] or to no observable effect [235–237]. Nonetheless, the use of distinct types of glucocorticoids and different dosing regimens render results hardly comparable. More standardized research is needed addressing the question of whether glucocorticoid administration modulates adiponectin levels, before conclusions regarding the HPA axis and sleep can be drawn [238]. To our knowledge, there is currently only one study investigating the direct association between sleep and adiponectin levels. In this investigation, experimental sleep restriction only decreased adiponectin levels in women but not in men [239].

Growth Hormone

Studies investigating how GH secretion is affected by sleep have previously been discussed in the relation to muscle mass. In this context, especially SWS has gained attention since it represents the window of most pronounced GH release [92, 240–242]. Selective SWS disruption by electrical stimulation [243] or natural reduction through ageing has been accompanied by reduced GH secretion [93], whereas SWS stimulation by pharmacological treatment led to increased GH secretion [94]. The following paragraph will discuss the effects of GH secretion on fat mass and whether targeting GH secretion by sleep modulation has the potential to improve body composition. Contrary to the anabolic effects of GH in most tissues (e.g., muscle), GH is involved in catabolic processes in adipose tissue [244] (see Fig. 3 as an overview of the effects of GH on body tissues). GH secretion in healthy individuals is negatively associated with the mass of adipose tissue,

especially visceral adipose tissue [245–248]. Decreased GH secretion is observed in obese, which manifests as a decline in the mass of GH secreted per burst [249, 250]. The central mechanism relating GH to the accumulation of adipose tissue lies in the induction of lipolysis, which forms the catabolic branch of fatty acid metabolism [251]. Lipolysis makes free fatty acids available for use when they are needed as substrates for lipid synthesis [244]. Induction of lipolysis has been shown to reduce adipose tissue mass, thus resulting in body fat mass reduction in both human [252] and animal studies [253]. Numerous studies have evaluated the potential of GH treatment as means to treat obesity [254–259]. There is mounting evidence that a GH-induced reduction in adipose tissue does not ultimately lead to a metabolically healthy tissue, but rather results in an unhealthy lean phenotype [246]. This counterintuitive difference between healthy obese and unhealthy lean needs further investigation and should be taken into account when considering GH augmentation as a means to improve body composition. It is noteworthy though that enhancing endogenous GH secretion has less adverse effects compared to exogenous GH administration [256, 259]. Hence, further research is needed investigating the possibility to increase endogenous GH secretion through sleep modulation and the potentially subsequent favourable changes in body fat mass.

Limitations and Implications

The number of studies investigating the relation between sleep and BMI exceeds studies assessing fat mass directly. Although BMI does not provide information about body mass composition due to its simplicity, it still often is the method of choice to assess someone's overweight or obesity. However, the strong positive correlation between body fat mass and BMI across the general population legitimates its use instead of body fat mass [37, 38, 260–263]. The variety and diversity of potential underlying mechanisms how body fat mass is related to sleep underlines the complexity of this field. Although it is likely that a multitude of mechanisms are involved, one big challenge is to elucidate their individual and causal impact. Furthermore, mechanisms leading to fat mass accumulation are likely to be highly versatile. Apart from molecular mechanisms relating to how ingested food is used and stored in our bodies, the regulation of appetite and satiety already starts beforehand. Moreover, regulation of food intake is not solely mediated by a homeostatic system but also by the hedonic system [264, 265]. The hedonic system refers to the concept that food intake can additionally be driven by the presence of highly palat-

able food that exert a highly rewarding experience. In the presence of such foods, the hedonic system can even abrogate the control by the homeostatic system [266]. Thus, it is not enough to exclusively focus on the actions of leptin, ghrelin, and other satiety signals to understand the drivers for eating. Further research, which also considers motivational and rewarding aspects of food intake and whether these mechanisms are influenced by sleep, is therefore needed.

Promising results obtained from a single animal study showed that adiponectin deserves further attention [227]. Here, researchers showed that slow wave enhancement inhibited the HPA axis, resulting in decreased cortisol secretion [267]. Thus, adiponectin concentration may change beneficially as well. Yet, there is need for future research directly examining the modulation of adiponectin levels through slow wave manipulation and its long-term consequences on fat tissue turnover. Although here we focus on the effect of sleep on body compositions and the underlying pathways, it should also be mentioned that there is evidence for a reciprocal interaction. One key example of this reciprocal interaction is obstructive sleep apnoea, a serious sleep disorder that causes breathing to repeatedly stop during sleep. While obesity is among the main risk factor for OSA, the disorder itself leads to a disturbed sleep ultimately altering energy balance resulting in further weight gain [268]. The polycystic ovary syndrome (PCOS) is another pathological condition that exemplifies the bidirectional relationship of altered sleep characteristics and body composition mediated by metabolic and endocrine changes. PCOS is an endocrine disorder affecting metabolic and reproductive processes [269]. Besides having a higher tendency to be overweight than the general population, sleep problems are frequently reported in patients with PCOS [270]. Although it is known that overweight may lead to sleep problems, overweight only partly accounts for the sleep problems in PCOS [270]. Various other mechanisms through which PCOS may lead to sleep disorders and disturbances have been proposed, including an upregulation of the HPA axis [271], increased androgen levels [270, 272], and insulin resistance [198, 273, 274]. However, the underlying mechanisms are probably much more complex and numerous, and not all of them are known yet. With OSA and PCOS here we just briefly discussed 2 examples that highlight the complexity of clearly distinguishing between the direction of the relationship between altered sleep characteristics and changes in body composition. To understand the reported associations on a mechanistic level, controlled experimental studies are needed.

Sleep and Bone Mass

Bone tissue is crucial for providing rigidity, strength, and shape and is essential for movement. Although bone tissue is a rigid structure, it undergoes dynamic changes, namely, the 2 processes formation (mediated by osteoblasts) and resorption (mediated by osteoclasts). Maintaining a constant bone mass requires a dynamic homeostasis between these opposing processes. Any imbalance, as it may occur with increasing age, altered sex hormone levels or the use of medication leads to a weakening of bone structure and increases the risk for fractures [275]. Bone health is usually assessed by DXA as bone mineral density (BMD) and bone mineral content (BMC), which both have been shown to decrease with age due to the imbalance in bone turnover [276]. Furthermore, BMD and BMC are reported to be lower in females compared to males [277], making gender and age factors requiring adjustment. BMD provides information for assessing bone fracture risk, whereas whole-body BMC is mainly height-dependent and not providing information about bone strength [278].

Restorative sleep is likely required to allow bones to recover from the pressure acting on them throughout the day. Yet, the underlying mechanisms how sleep affects bone homeostasis are complex and largely unknown. Evidence that sleep and bone health are related is mainly derived from studies assessing the quality and duration of sleep together with BMD assessments. Both long [279–284] and short sleep duration [281, 282, 285–292] have repeatedly been associated with low BMD and osteoporosis. However, a meta-analysis found that only long sleep duration (≥ 8 h/day) was associated with a 22% higher risk of osteoporosis, while no association between short sleep and osteoporosis was found [293]. Furthermore, some studies found no association between sleep duration and BMD [74, 294]. Additional investigations examined whether subjective sleep quality, assessed by PSQI, was associated with bone health. Here, poor subjective sleep quality was found to negatively correlate with BMC and BMD [74, 184, 295]. One major limitation of these studies is the subjective report of sleep duration and quality, thereby making the results hardly comparable between individuals. In addition, objective sleep quality assessed by an accelerometer was not associated with any bone health parameter [184]. Taken together, there is currently much inconsistency in this area of research pointing to the need of further research as well as for controlled experiments with objective sleep parameters (e.g., PSG-assessed macro- and microstructure aspects of sleep).

Underlying Mechanisms

The underlying mechanisms on how poor sleep quality and/or sleep duration may negatively affect bone health are likely to be versatile [184]. Several mechanisms linking various sleep variables to bone turnover have been suggested and will be discussed in the following paragraphs. Figure 1 provides a graphical overview of those potential mechanisms.

Bone Turnover Markers

A useful means to examine mechanisms by which sleep affects bone health are bone turnover markers (BTMs) measurable in blood in response to bone resorption, bone formation, or cytokine function.

Swanson et al. [296] investigated the impact of a combined sleep restriction and circadian disruption intervention on 4 BTMs: C-terminal cross-linked telopeptide of type I collagen (CTX), which is indicative for bone resorption, N-terminal pro-peptide of type I procollagen (P1NP), a biomarker for bone formation, sclerostin, and fibroblast growth factor 23 (FGF-23), 2 biomarkers for osteocyte function. Participants underwent an intervention including sleep restriction to 5.6 h/night in combination with forced circadian-desynchrony, which was provoked by 28 h-days for 3 weeks. They reported P1NP to be significantly lower post-intervention than baseline levels, with a more pronounced effect in younger subjects (<28 years) than in older subjects (>55 years). A significant increase and decrease in response to the intervention were observed for sclerostin and FGF-23, respectively. While the increase in sclerostin was only observed for the younger group, the change in FGF-23 levels was observable among all participants. CTX was not affected by the intervention [296]. Interestingly, P1NP levels declined significantly from the first day of intervention and stayed at almost constant lower levels during the following 3 weeks [297].

Among BTMs, CXT displays the most robust 24 h circadian rhythm [296, 298–300] with generally higher levels observed in women than in men [301]. However, the shape of the 24 h profile of bone resorption parameters such as CTX does not seem to be influenced by sex [302, 303], age [302], posture [302], or parathyroid hormone [304]. In addition, fasting has been identified as a factor that diminishes the amplitude of the CTX concentration rhythms but does not change the 24-h profile [302, 305, 306]. P1NP on the other hand does not seem to follow a clear circadian rhythm [307–309] and is relatively insensitive to food intake [310], thereby rendering P1NP a suitable biomarker for investigating the effect of sleep restric-

tion or deprivation. The distinctive sinusoidal rhythm across the 24 h of a day, as for instance observed in CTX, is likely due to the presence of peripheral oscillators as suggested by the expression of clock genes in bone tissue [311–314]. Sleep restriction or deprivation or the shift of sleep timing as it may occur in night shift work can therefore potentially lead to a disrupted rhythmicity of BTMs and may subsequently result in impaired bone health due to an imbalance between bone formation and bone resorption. Observations made among night shift workers support this mechanism [315, 316], as for instance reported in postmenopausal female rotating-shift nurses that showed lower BMD at lumbar spine and at femoral neck than those that worked daytime shifts [315].

Inflammation

The presence of an inflammatory microenvironment, especially if persisting over a long time, is known to negatively influence bone metabolism by disturbing the balance between bone-resorbing osteoclasts and bone-forming osteoblasts, finally resulting in bone loss [317]. A system centrally involved in the regulation of bone turnover is the RANKL/OPG system, which was shown to be highly sensitive to inflammation [317]. Binding of RANKL to osteoblasts induces a signalling cascade, ultimately leading to the differentiation of osteoclasts [318]. While under physiological conditions osteoclast differentiation is tightly controlled through the inhibitory effect of OPG, this system is disturbed in an inflammatory response.

Rheumatoid arthritis (RA) is one example for a chronic inflammatory disease, which leads to a constant secretion of pro-inflammatory cytokines and thereby serves as a model to investigate the effect of inflammation on bone mass. The secreted pro-inflammatory cytokines in RA include IL-6, IL-1, IL-17, and TNF- α . These cytokines lead to an enhanced osteoclastogenesis, mainly mediated by their activating effect on RANKL [162, 319]. Moreover, besides the secretion of resorption-promoting cytokines, RANKL secretion itself is enhanced. This in turn leads to a change in the RANKL/OPG ratio and ultimately interference with the fine-tuned balance between bone formation and bone resorption [317].

While so far much of the research has focussed on an inherited autoimmune disease, it remains to be elucidated what other factors can cause the presence of a persisting inflammatory bone microenvironment. Noteworthy, very little research has been conducted in the area investigating whether sleep has any influence on inflammation processes in bone tissue. While no human study exists yet, an experiment in rodents found an increased ex-

pression of IL-1 β , TNF- α , and RANKL in the temporomandibular joint of animals that were paradoxical (REM) sleep-deprived compared to the control group, indicating an impaired bone metabolism [320]. More research is needed to further examine the relevance of inflammation on bone metabolism altered by sleep variables. Potential candidates are IL-6 and TNF- α , and both pro-inflammatory cytokines were previously shown to be increased in healthy young adults who had their sleep restricted to 6 h per night [321]. Importantly, inflammation is not bad per se and should not be generally thought to interfere with bone health. Inflammatory mediators are part of the normal healing response or are needed as an immune response towards pathogens. However, chronic inflammation or an increase of inflammatory markers over prolonged time periods might negatively affect bone turnover. Consequently, future studies assessing sleep-related changes in inflammation markers and their role in bone turnover should include long-term investigations.

Autonomic Nervous System Activity

Another potential link between sleep and bone health is the autonomic nervous system (ANS). For instance, short sleep was found to be associated with sympathetic nervous system (SNS) hyperactivity [288], which in turn was shown to favour low bone mass [322]. Likewise, also the second branch of the ANS, the parasympathetic nervous system (PNS), might affect bone metabolism with opposite effects [323]. Concordantly, sectioning PNS fibres in rodents was observed to result in low bone mass [324].

The main neurotransmitter of the SNS is norepinephrine, which exerts its function via α - and β -adrenergic receptors. Bone cells show mainly an expression of β -adrenergic receptors and rodent studies showed that daily stimulation of these resulted in increased bone catabolism characterized by enhanced osteoclast formation, a reduction in the function of osteoblasts, and finally in bone loss [325–328]. In addition, selective blockade of these receptors in young mice increased bone-forming activity, ultimately leading to a higher observed bone mass [328–330]. In contrast, PNS activity is suggested to have a favourable influence on bone mass via direct action of acetylcholine on osteoclasts and osteoblasts as well as through the suppressive effect on sympathetic activity on bone receptor levels [331–333]. Sharing neurophysiological and chemical mechanisms, autonomic regulation, and sleep is tightly linked on the anatomical as well as on the physiological level [149]. Transitions be-

tween sleep stages are characterized by coincidentally fluctuating ANS activity [334]. The parasympathetic tone increases during N2 and N3 sleep compared to wake [335], whereas the sympathetic tone decreases [336]. Moreover, while NREM sleep is clearly characterized by parasympathetic predominance, sympathetic activity dominates during REM sleep [336]. The SNS activity was even shown to exceed the sympathetic activity during wake [337]. Recently, experimental enhancement of SWA by auditory stimulation was shown to increase parasympathetic activity during SWS [149]. SWS-mediated changes in ANS activity are thought to influence several physiological processes including glucose metabolism [338], immune [339], and cognitive functions [340]. Therefore, the characteristic predominance of parasympathetic activity together with low sympathetic tone during SWS may represent a favourable window for bone formation.

IGF-1/GH

As previously discussed, GH and ultimately IGF-1 secretion are strongly influenced by SWS. However, the importance of GH is not restricted to muscle tissue only but is likewise involved in growth mechanisms in other tissues, including bone (see Fig. 3 for an overview). In experimental studies, administration of both, GH and IGF-1, was found to stimulate the growth of longitudinal bones in animals and humans by direct action [341, 342] as well as indirectly by increasing the production of IGF-1 [342, 343]. Additional evidence supporting the critical effect of GH on bone mass comes from studies investigating the effects of GHD [344]. It was shown that a lack of GH and simultaneous low levels of IGF-1 in mice with mutation in the GHRH receptor were associated with osteopenia and reduced cortical bone mass. Exogenously administered IGF-1 did almost completely reverse the negative effect on bone growth [344]. Moreover, in patients suffering from adult growth hormone deficiency, treatment with GH resulted in an increase of BMD [345, 346]. Therefore, when present at subphysiological levels, GH administration seems to be beneficial in terms of promoting bone health and increasing BMD. However, whether this effect is of great importance under physiological levels remains to be elucidated. Nevertheless, evidence from experimental studies in osteoporotic subjects as well as in patients with bone fractures revealed a significant positive effect of GH or IGF-1 administration on bone health [347, 348]. IGF-1 administration in healthy and osteoporotic females was found to increase bone formation in several studies, including different dosing reg-

imens and durations varying from 6 days to 9 months [349–354]. Since GH/IGF-1 is known to be involved in mechanisms that are impaired in delayed or failed bone fracture healing, several clinical trials investigated the effect of GH/IGF-1 administration on fractured bone healing. They reported increased BMD, better functional recovery, as well as increased bone strength [354–356]. Based on experiments that found a significant association between SWS and GH secretion [91–94], sleep modulation may support bone mass preservation in osteoporotic people as well as in the healing process following a bone fracture.

Leptin

Although leptin is primarily known for its central role in the regulation of energy homeostasis, its involvement in bone metabolism receives increasing attention. First evidence showed that leptin-deficient mice had higher vertebral trabecular bone mass than wild-type mice [357]. Over the years, further evidence emerged that leptin acts centrally as well as peripherally to control bone mass [358–361]. This has risen the question on how the communication between cells in the brain and bone cells is possible. Therefore, a mice parabiosis model was used to determine whether the factor leading to low bone mass phenotype could be exchanged via circulation or whether it was of neural origin. Seeing that only the animals that got leptin delivered into the third cerebral ventricle did show low bone mass, the mediator was suggested to be a signal of neural nature [357]. As already discussed in relation to body fat mass, leptin levels have repeatedly been shown to be sensitive to short sleep as well as to single sleep stages [176, 178, 206, 207]. Therefore, further research investigating leptin concentration in response to sleep in general and to the modulation of sleep, more specifically, should consider that leptin is also crucially involved in bone metabolism apart from its central role in energy homeostasis.

Limitations and Implications

Although many studies only focused on total sleep duration or sleep quality so far, some pathways have been suggested, which are likely involved in bone turnover and which are affected by a variety of sleep parameters. Activity of the ANS, for example, may play an important role in bone metabolism as sympathetic activity was shown to dominate during REM sleep [337] and to be associated with bone resorption [325–328]. Moreover, BTMs' characteristic for bone resorption displays a peak in the second half of the night when REM sleep predominates

[302]. PNS as counterpart of the SNS predominates during SWS [335] and was proven beneficial for bone formation [331]. Taken together, either selectively intensifying NREM sleep (SWS enhancement) or decreasing the proportion of REM sleep without changing total sleep duration may represent potential approaches to shift the activity of the nervous system more towards parasympathetic activity and subsequently the balance of bone metabolism more towards bone formation. While methods to enhance and intensify SWA exist and have previously already been discussed, suppression of REM sleep is a less typical experimental approach but is a commonly observable phenomenon in people taking antidepressants [362]. Therefore, further investigations are needed focusing on the association between sleep architecture and bone health in more detail. Identification of a specific sleep micro- or macrostructural feature that is especially critical in bone metabolism may represent a target for selective modulation in order to increment parasympathetic activity during sleep.

Moreover, leptin and GH/IGF-1 are likely to be further mechanisms involved in the link between sleep and bone health. While balanced leptin concentration importantly contributes to a healthy bone metabolism [357–361], dysregulated leptin levels as a consequence of short sleep [178, 206, 207] may negatively affect bone mass. However, whether the modulations in leptin levels caused by changes in sleep duration are relevant for bone turnover needs to be further investigated. The relevance of GH/IGF-1, on the other hand, has previously been shown to be of clinical importance in the pathology of osteoporosis [349–354], after bone fractures [354–356], and is likely to affect GH secretion [91–94]. Further controlled studies over an extended period are required to explore whether GH levels can be increased to clinically significant levels by sleep modulation and whether this increase translates into improved BMD.

Metabolic System under Challenge: The Role of Sleep

The previous paragraphs on the role of sleep in metabolic processes mainly summarized current evidence under resting conditions. Yet, sleep might become specifically important at times when the metabolic system is challenged, such as induced by physical exercise, during a weight reduction diet, or when bones are fractured. Here, we focus on the potential interplay of sleep with these challenges.

Promoting Muscle Anabolism: Physical Exercise and the Role of Sleep

Physical exercise, especially resistance training, is widely accepted as the main strategy to induce muscle hypertrophy and improve musculoskeletal health [363, 364]. A single bout of resistance exercise has consistently been shown to trigger muscle protein synthesis, resulting in a net protein balance when combined with protein intake [365, 366]. Resistance exercise enhances the ability for skeletal muscle cells to sense amino acids [367], ensuring an adequate rise in postprandial muscle protein synthesis and accretion of muscle tissue when the exercise regimen is sufficiently repeated over time [368]. Nutrition and muscle contraction work in synergy to augment post-exercise increases in muscle protein synthesis and mass on the longer term, but the influence of sleep has been neglected so far.

Intriguingly, a recent study showed that short-term sleep deprivation leads to lower rates of myofibrillar protein synthesis in the basal, non-exercised state. However, when subjects performed high-intensity interval training during this 5-day period of sleep deprivation, myofibrillar protein synthesis rates were maintained at control levels, suggesting that high-intensity muscle contractions can overcome the negative effects of sleep deprivation on muscle architecture [369]. In line with these data, a 96-h period of sleep deprivation in rats resulted in ~5% muscle atrophy over the course of 8 weeks, while resistance training in the form of weighted ladder training attenuated the reduction in muscle fibre cross-sectional area [370].

Given the increasing prevalence of inadequate sleep in modern societies, future efforts should be directed to better understanding the mechanisms underlying the profound effects of sleep deprivation on basal muscle protein synthetic rates. In the long run, the gained knowledge could be used to optimize interventions to reduce the negative effects of sleep deprivation on muscle health. For instance, overnight sleep is the longest post-absorptive phase across the 24 h of a day and emerging evidence suggests that pre-sleep protein intake can enhance positive effects on muscle remodelling both acutely [371–374] and in the longer term [375, 376]. Hence, potential exciting areas of interest include the optimization of pre-sleep protein beverages in terms of amino acid composition and absorbability that improve net protein balance in sleep-restricted situations. Additionally, given the profound effects of muscular contractions on muscle protein synthesis, future research should focus on the promotion of exercise regimens that are tolerable in a sleep-deprived state.

The Role of Sleep for Successful Weight Loss and Weight Loss Maintenance

Given that both short sleep duration and obesity are increasingly prevalent in modern societies, investigating the importance of sleep for weight loss is of high interest for public health [377]. Subjectively reported sleep quality and quantity prior to weight loss interventions were shown to be associated with the success of the intervention and subsequent maintenance of lost weight [378]. Furthermore, worse sleep quality at 6 months after the intervention decreased the likelihood of successful weight loss or maintenance of lost weight at 18 months [378]. Among the objectively actigraphy-assessed sleep parameters, only sleep duration significantly correlated with the amount of maintained weight loss [379]. Comparing a group of subjects undergoing calorie restriction (CR) to another group in which CR was combined with sleep restriction (decreased habitual sleep duration of 1 h per day on 5 days/week), this study aimed to determine whether the association between sleep duration and weight loss can also be found in an experimental design. Although both groups lost similar amounts of weight, the proportion of weight lost as fat was significantly higher in the CR group that had an unchanged sleep duration [380]. Another study with a daily calorie deficit of 600–700 kcal/day over a period of 15–24 weeks led to a mean weight loss of 4.5 ± 3.9 kg. Interestingly, subjectively reported sleep duration at the beginning of the experiment was found to be positively correlated with the proportion of weight loss coming from fat stores [381]. Although studies investigating the association between sleep duration and the success of weight loss predominate, results from a study by Verhoef et al. [382] also propose the presence of a relationship in the opposite direction. Here, changes in sleep duration were assessed during a 3-month weight loss intervention in obese volunteers. Subjectively classified short sleepers at baseline, who successfully lost weight, had significantly increased their sleep duration with weight loss. These results imply a bidirectional relationship between sleep duration and weight loss and both seem to benefit from each other [382]. Taken together, sleep may represent a modifiable factor that should be considered in weight loss programs and that may additionally facilitate the success of the intervention. Yet, more research is needed to identify which sleep aspects and underlying mechanisms efficiently support weight loss.

The Role of Sleep in Bone Fracture Healing

Bone fractures are among the most common injuries of the musculoskeletal system and thus affect a great

number of people [383]. Essentially, the demographic shift towards an ageing population contributes to the increasing prevalence of fragility fractures [384]. Although bone tissue has a unique capacity for repair, a substantial proportion of fractures result in non-union or delayed healing [385]. Thus, several factors have been identified that determine the chance of successful healing response: fracture type, age, treatment, medication, alcohol, and smoking [386]. Evidence from animal studies showed that sleep deprivation in rats resulted in a decreased BMD, decreased osteogenesis, and impaired bone mineralization [387], which may indicate that sleep is another factor determining risk for incomplete or delayed healing. A rodent study inducing femur fracture together with experimentally induced sleep deprivation supports the central role of sleep for the healing process as sleep deprivation was found to delay bone fracture healing and significantly increase levels of the pro-inflammatory cytokines IL-1 β and TNF- α [388], which are in line with findings from previous studies [389]. Treatment with the anti-inflammatory drug trehalose substantially mitigated the negative effects of sleep deprivation on bone recovery [388]. Taken together, observations from rodent studies imply that sleeping enough is crucial during bone fracture recovery. However, the fact that evidence is restricted to animal studies represents a major limitation to the relationship between sleep and human bone healing. Therefore, further research in humans is needed to translate the significance of this observation to human bone fractures. Nevertheless, as experimentally induced fractures in humans are not feasible, epidemiological studies recruiting patients with fractures should be considered to investigate the role of sleep on the healing process and success.

Limitation of the Present Work and Implications for Further Research

For all reviewed body composition parameters, muscle mass, bone mass, and body fat mass, a link to sleep has previously been documented. Yet, there have been several limitations that render definite conclusions difficult.

First, in most of the presented studies, body composition, sleep, or both were assessed with inaccurate methods. Therefore, many sleep studies collected rather anthropometric than body composition data or several studies that accurately measured body composition with DXA or BIA assessed sleep solely with subjective sleep questionnaires such as the PSQI. Furthermore, previous work has often only been limited to total sleep duration

and its association with symptoms or diseases. Thus, accurately examining body composition by DXA and acquiring sleep data via PSG, which allows the identification of sleep architecture even on a topographical level when assessed with high-density EEG, may have a promising potential for the identification of relationships between sleep and body composition.

Second, the number of observational studies exceeded the number of controlled experiments by far. Investigating the associations between sleep variables and body composition parameters or specific molecules does not give any information about a causal relationship. To draw valid conclusions about mechanisms, more controlled experimental studies that manipulate sleep are needed. There is evidence for some pathways, suggesting that the amount of SWS is of particular importance. Therefore, selective enhancement of slow waves and increasing SWS percentage over the course of a night without changing total sleep duration represents an interesting and promising approach for further pursuit. In the early years of this research field, mainly pharmacological approaches were used, which were shown to effectively decrease daytime sleepiness in sleep-restricted individuals [267]. However, since pharmacological approaches entail the problems of tolerance and dependence, over the years additional non-invasive methods have been established. Promising avenues to modulate slow waves include slow oscillatory transcranial direct current stimulation [263], transcranial magnetic stimulation [270], and sensory stimuli such as auditory (closed-loop) stimulation [390]. To date, auditory stimulation represents the most promising approach because of its low costs, safety, scalability for long term, and mobile use in ambulatory studies as well as artefact-free EEG recordings [391]. Even though this method is still in its infancy, some well-controlled in-lab studies exist, which showed its potential in boosting slow waves along with modifications in memory consolidation, cortisol levels [95], and immune supportive responses [95]. Single session glucose tolerance and GH levels in healthy young adults were not effectively modulated so far [95, 392]. However, further research over longer time periods and in populations/situations of increased metabolic demand (e.g., elderly, athletes, and obese) is essential to evaluate its potential to modulate certain metabolic pathways. Finding a means to modulate sleep in such a way that it has a beneficial consequence on body composition is a potential breakthrough in the treatment of various disabling diseases and concurrently would also massively decrease the burden on health costs. Furthermore, we need to con-

sider that various research models including in vitro studies, different in vivo animal studies, and well-controlled human laboratory studies up to large-scale cohort assessments and meta-analyses provide different levels of evidence (e.g., mechanistic insights and societal impact). Therefore, an interdisciplinary approach leveraging on studies that span different research models and techniques will be important to establish a comprehensive understanding of the role of sleep in metabolism from a mechanistic to a societal perspective.

Third, even though sleep restriction/deprivation studies primarily define the role of sleep in certain processes, a complete separation of circadian influences is not possible since these processes are not completely independent [393]. The inclusion of circadian control parameters and studies that subtly alter parameters of sleep (e.g., enhance amount of deep sleep, modulate REM sleep) instead of modifying sleep duration could help to disentangle the direct role of specific sleep characteristics (rather than indirect changes over circadian modifications) in metabolism.

Finally, while this review summarizes a collection of publications showing links between sleep and body compositions or metabolic processes (implied in body composition), it is largely unknown whether prolonged changes of metabolic processes through sleep modification/changes will translate into significant body composition adaptations. Moreover, the effect of sleep or sleep modulation may be different under baseline conditions and when the metabolic systems are challenged or in a pathological state. Studies identifying the translational potential of metabolic changes through sleep in different contexts will be of utmost importance and require well-controlled, long-term trials including sleep modulation, molecular assessments, and accurate sleep and body composition tracking. Long-term assessment and modulation of sleep represent a challenge as these sleep studies are costly and time-consuming for the experimenter and the participants. Nevertheless, the recent development of research-grade, mobile PSG, and sleep modulation systems allows for accurate in-home assessment and modulation of sleep [391] and opens up new possibilities to perform these long-term trials.

Concluding Remarks

Unhealthy body composition such as an excessive accumulation of adipose tissue considerably impairs overall health. However, while mainly diet and the lack of physi-

cal activity seem to cause excessive body fat, sleep is much less seen as a causal risk factor. Similar to muscle mass and bone metabolism, sleep has not received its deserved attention so far.

Here we aimed to provide a review covering the evidence in the field of sleep and body composition parameters including muscle mass, body fat mass, and bone tissue. In addition, we investigated potential mechanisms how sleep architecture, sleep duration, and sleep oscillations may critically influence human body composition. The identification of mechanisms how sleep is associated with changes in body composition represents a target for modulation, thereby promising beneficial consequences for general human health. Some mechanisms that could potentially link sleep and body composition have already been identified. Interestingly, among the described pathways, GH was found to be involved in the homeostasis of all discussed body composition parameters and has been strongly linked to sleep, specifically SWS (see Fig. 3). Therefore, SWS seems to play a key role in connecting sleep to body composition and should be a focus of well-controlled future studies. Specifically, its importance under baseline physiological and under pathological conditions in relation to sleep is of fundamental interest.

The identification of sleep parameters that critically impact key regulators of either type of body mass has a great potential as a target for new treatment options for diseases and disorders related to unfavourable body composition. As shown with the example of obesity, it is not only the condition itself but the numerous disabling comorbidities making obesity a global major health problem. Although muscle atrophy and decreased bone mass affect less people than an unhealthy body fat distribution, both changes in muscle and bone mass may lead to further comorbidities as well. We therefore argue that further research is needed investigating how the modulation of sleep (e.g., sleep oscillations and sleep stages) can positively affect human health through a favourable body composition. Well-controlled, long-term studies in humans and animal models are required to make conclusive statements.

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Statement of Ethics

An ethics statement is not applicable because this review is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.M.S., S.H., G.D., and C.L. took part in conceptualization of this review. F.M.S. wrote the first draft of the manuscript. S.H., G.D., and C.L. reviewed and edited the manuscript. All authors revised the manuscript critically for important intellectual content and approved this version of the manuscript to be published.

Data Availability Statement

Data availability is not applicable to this article as no datasets were generated or analyzed for this review article.

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